

Government of Pakistan
(MINISTRY OF NATIONAL HEALTH SERVICES, REGULATIONS AND COORDINATION)
(Drug Regulatory Authority of Pakistan)

Islamabad, the June 05th, 2018

NOTIFICATION

S.R.O. 697 (I)/2018. – In exercise of the powers conferred by section 23 of the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012), the Drug Regulatory Authority of Pakistan, with the approval of the Federal Government, is pleased to make the following rules, namely:-

1. Short title and commencement. - (1) These rules may be called the Bio-study Rules, 2017.

(2) They shall apply to all contract research organizations, laboratories for clinical research, bio-availability and bio-equivalence study centers or organizations operating in public or private sector, involved in clinical trials of therapeutic goods and bio-availability or bio-equivalence studies on human subjects.

(3) They shall come into force at once.

2. Definitions.– (1) In these rules, unless there is anything repugnant in the subject or context,-

(a) “Act” means the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012);

(b) “adverse reaction” means any untoward and unintended responses to an investigational medicinal product related to any dose administered;

(c) “adverse event” or “AE” means any untoward medical occurrence in a patient or clinical investigation subject, to administered investigational product and which does not necessarily have a causal relationship with this treatment;

(d) “bio-availability” or “BA” means the therapeutically active fraction of administered drug that reaches the systemic circulation;

- (e) “bio-equivalence “or “BE” means bio-equivalence phenomenon, according to which two medicinal products containing same pharmaceutical formulation and quantity of the same active ingredient, are considered bioequivalent if they are pharmaceutically equivalent and their bio-availabilities, in terms of rate and extent, after administration in the same molar dose, lie within acceptable predefined limits;
- (f) “center” means bioavailability or bioequivalence studies center owned by public or private sector dully licensed by the DRAP;
- (g) “clinical studies committee” or “CSC” means a committee constituted under rule 13;
- (h) “clinical trial” or “clinical study” means any investigation in human subjects intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of an investigational product or to identify any adverse reactions to an investigational product or to study absorption, distribution, metabolism and excretion of an investigational product with the object of ascertaining its safety and efficacy;
- (i) “contract research organization” or “CRO” means person or organization contracted by the sponsor, for purpose to perform one or more of its trial related activities and functions;
- (j) “good clinical practice” or “GCP guidelines” means good clinical practice guidelines issued under rule 15, to set a standard for the design, conduct, performance, monitoring, auditing, recording, analyzing and reporting of clinical trials;
- (k) “independent ethics committee” or “IEC” means an independent body constituted of medical professionals and non-medical members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection by among other things, reviewing and approving or providing favourable opinion on the trial protocol, the suitability of the investigators, facilities, methods and material to be used in obtaining and documenting informed consent of the trial subjects;
- (l) “ICH” means International Council for Harmonization;
- (m) “informed consent” means a process by which a subject voluntarily confirms his willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. It is documented by means of a written, signed and dated informed consent form;
- (n) “institution” means any medical institution for public or private entity or agency or medical or dental facility dully registered by medical and dental council where clinical trials are proposed to be conducted;

- (o) “IRB” means Institutional Review Board as provided under rule 9.
- (p) “investigational product” means investigational therapeutic goods or pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled or formulated or packaged in a way different from the approved form or when used for an unapproved indication or when used to gain further information about an approved use;
- (q) “laboratory” means bio-analytical laboratory for activities and services related to clinical trial and BA or BE studies; and
- (r) “trial subject”.-means an individual who participates in a clinical trial, BA or BE study, either as a recipient of the investigational products or as a control.

(2) The terms used but not defined herein shall have the same meanings as one assigned to them by the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012) and the Drugs Act, 1976 (XXXI of 1976).

3. **Application and issuance of license.-** (1) An application for the purpose of license to act as CRO, clinical trial site, BA and BE center or laboratory, as the case may be, shall be submitted on Form-I, addressed to the Chairman or Secretary of CSC.

(2) Every such application shall be accompanied with all the necessary records, information, documents, data and a non-refundable fee as specified under the Act. The fee shall be paid in the bank account of DRAP. Incomplete applications shall not be received.

(3) The received application shall be processed and scrutinized by the Division of Pharmacy Services.

(4) Once the application is thoroughly reviewed and evaluated by the concerned section, it shall be placed before the CSC in its very next meeting for the consideration.

(5) CSC after reviewing the application shall decide to approve or reject the application, keeping in view the public interest.

(6) Before issuance or renewal of license, the CSC shall satisfy itself that the conditions of license, as mentioned under rule 4, are complied with by the applicant.

(7) Certificate of license to act as BA and BE center, shall be issued on Form – IV.

(8) Certificate of license to act as CRO, clinical trial site or laboratory, as the case may be, shall be issued on Form – V.

(9) An applicant who is not satisfied with the decision of the CSC, may file an appeal under rule 23.

4. Conditions for license.- (1) The applicant shall provide premises which shall be suitable for intended use, in size and construction and shall be located in an area free from offensive and obnoxious odours and other possible sources of contamination. The premises must have protective equipment for personnel and emergency firefighting arrangements.

(2) The applicant shall provide adequate space, facilities and equipment for the conduct of intended operations.

(3) The clinical trial, BA, BE, Bio-analysis activities shall be conducted under the active directions and personal supervision of competent technical staff consisting of at least one person holding a degree in the field of medical sciences from a recognized university in Pakistan or abroad and shall possess qualifications and experience which, in the opinion of the CSC, is appropriate and adequate for the purpose.

(4) Sufficient clinical support staff including phlebotomists duly qualified for the purpose must be available at the facility.

(5) The applicant shall ensure that,-

(a) the staff involved in the clinical trial, BA, BE, Bio-analysis activities is fully

trained in accordance with GCP and good laboratory practices (GLP) guidelines;

(b) audit procedures are pre-defined and relevant SOPs and guidelines are in place;

(c) the licensed premises shall only be used for which it has been authorized by the licensing authority;

(d) the licensed premises are maintained properly and shall, as far as possible, be orderly, clean and free from accumulated waste and vermin;

(e) unhygienic practices eating and smoking shall not take place in the area where research work is being conducted;

(f) sufficiently clean, appropriately ventilated toilet facilities, including facilities for washing and room for changing clothes, shall be available for the use of personnel where required;

(g) hygienic garments shall be worn by all staff in laboratory;

- (h) high standard of personnel hygiene shall be observed by all persons concerned with research work; and
- (i) no person known to be suffering from communicable disease or to be a carrier of such a disease and no person with open lesions or skin infection shall be engaged in research activities.

(6) The applicant shall provide-

- (a) adequate facilities for first aid and emergency medical treatment for the staff and trial subjects, including ambulance facility to transfer critical cases to the authorized tertiary care hospitals;
- (b) medical inspection of workers at the time of employment and periodical checkup thereafter at least once a year;
- (c) facilities for vaccination and inoculation against the enteric or any other epidemic group of diseases; and
- (d) adequate precautions for safe-guarding the health of the workers, including measures to avoid accidents or diseases.

(7) Such other condition as required or advised by the CSC, keeping in view the nature of the case.

5. Duration of license. - A license, issued in consequence of the application, shall, unless earlier suspended or cancelled, will remain in force for a period of three years from date of issuance.

6. Renewal of license. - License holder shall apply for renewal of license three months before the expiry of the validity period along with prescribed fee for renewal. A grace period of sixty days shall be permissible along with submission of late fee as specified under the Act and any such application for the renewal shall not be entertained after expiry of that period. However, applicant can apply for fresh license with full fee if so required.

7. Application and approval of clinical trial, BA or BE study.- (1) Application for approval or registration of clinical trial and BA or BE study shall be made on application Form-II and Form-IIA respectively, addressed to the Chairman or Secretary, CSC.

(2) Every such application shall be accompanied with all the necessary records, information, documents, data and a non-refundable fee as specified under the Act. The fee shall be paid in the bank account of DRAP along with required documents or information as per Appendix -A and Appendix -B. Incomplete applications shall not be received.

(3) The received application shall be processed and scrutinized by the Division of Pharmacy

Services.

(4) The application, if required, may be reviewed by experts appointed by DRAP. There shall be confidentiality agreement with the reviewers and the members of CSC, to ensure that the content of the application remains confidential.

(5) The initial review may result in queries that need to be answered by the applicant. The reviewers shall not be permitted to directly contact the applicant and all correspondence should be through DRAP.

(6) The reviewers or assessors may also ask for the pre-clinical data related to the clinical trial application from the applicant.

(7) The reviewers shall generate a report that shall be presented to the CSC along with the application.

(8) Once the application is thoroughly reviewed and evaluated by the concerned section and assessor finds that no further clarification or technical opinion of the expert is required, it shall be placed, with all the data, before the CSC in its very next meeting for the consideration.

(9) CSC after reviewing the application shall decide to approve or reject the application, keeping in view the public interest.

(10) CSC may process the application of a clinical trial on fast-track basis if it feels necessary to do so in the best public interest or in public health emergency cases, after recording the reason therefore.

(11) Certificate of approval of clinical trial, BA or BE study, as the case may be, shall be issued on Form – VI.

(12) An applicant who is not satisfied with the decision of the CSC may file an appeal under rule 23.

8. Conditions for clinical trials and BA or BE studies.- (1) The investigational product or trial material shall bear a label to state “caution: for investigational use only”, and "Not for sale".

(2) The investigational product must have been produced by the manufacturer in compliance to the current good manufacturing practices.

(3) Quarterly report of results obtained during clinical trials shall be furnished to the CSC.

- (4) Ethical criteria for the clinical trials or studies, as defined under Pakistan good clinical practices or ICH GCP or WHO guidelines, must be fulfilled.
- (5) Any adverse reaction shall be reported immediately to the concerned section of the DRAP.
- (6) The final results of the clinical trial, BA or BE studies, must be communicated to the CSC, at the completion of the investigation.
- (7) The sponsors and the investigators shall make themselves bound to permit access of any nominated officers of the DRAP, at reasonable times to copy and verify any records and reports relating to the clinical investigation.
- (8) The progress report of clinical trial or studies should contain sufficient information required to access the safety to subjects of the clinical investigations.
- (9) The clinical investigations should not be conducted in a manner substantially different than described in the protocols submitted with the application for approval of the clinical trials or studies.
- (10) No amendments in the approved protocol of trial or study can be made without seeking prior approval from CSC.
- (11) Any amendment or report to the investigational study, shall not contain any intrigue statement of material fact or omit material information required by this part as Pakistan GCP or ICH GCP guidelines.
- (12) The investigational product shall not be promoted or distributed for commercial purposes and quantities should be justified by the requirement of investigational study or clinical trials.
- (13) The destruction of unused investigational products should be carried out after seeking approval from CSC which shall nominate officers to accompany during the process of destruction of investigational products.
- (14) On a notice by the DRAP, the sponsor shall provide written explanation or correction in writing, for any required information.
- (15) The provisions of ethics committee or IRB shall strictly be complied.
- (16) During monitoring, one or more officers from DRAP shall accompany the monitoring team. The monitoring cell of trial or study shall intimate CSC well in time to depute suitable officers to join the monitoring inspection.

(17) Any information related to the trial or study that has an important bearing on the benefit-risk assessment of the investigational product or that would be sufficient to consider changes to the overall conduct of the clinical trial, requires to be communicated immediately with CSC.

(18) The investigators shall maintain the database of subjects recruited or enrolled for the study or trial, comprising of information including name, father name, age, gender, CNIC number, address and previous trial or study participation history and shall submit the same in soft and hard form to the DRAP.

(19) The CSC may terminate clinical trial, BA or BE study approval, if;

- (a) the sponsor and investigators fail to promptly investigate and inform the CSC for serious or unexpected adverse experiences in accordance with Pakistan GCP or ICH GCP guidelines or fail to make any other report required under this part;
- (b) the sponsor or investigator fails to submit an accurate progress report of the investigations in accordance with Pakistan GCP or ICH GCP guidelines; and
- (c) the sponsor or investigator fails to comply with any other applicable requirements of these rules and Pakistan GCP or ICH GCP guidelines.

(20) Such other condition as required or advised by the CSC, keeping in view the nature of the case.

9. Ethical clearance. (1) It shall be mandatory for the applicants who are willing to conduct clinical trials or studies, to seek prior approval from IRB of medical teaching institutions and National bioethics committee (NBC) of Pakistan.

(2) The IRB should consist of following number of members, who collectively have the qualifications and experience to review and evaluate the science, medical, legal aspects and ethics of the proposed trial. The IRB should include,-

- (a) at least five members;
- (b) at least one member whose primary area of interest is in a non-scientific area; and
- (c) at least one member who is independent of the institution or trial site.

(3) No person involved in clinical trial or BA or BE study shall be part of IRB and independent ethics committee or NBC.

(4) The funding and source of funding of IRB and its members be clearly defined and documented.

(5) The IRB shall be responsible for the periodic review of the clinical trial or BA or BE study, as the case may be, and submission of their reports to the CSC.

10. Labeling requirements for investigational products.- The immediate package of an investigational product intended for human use, shall bear a label with the statement “caution: For investigational use only” and "Not for Sale", prominently. The label or labeling of the investigational product shall not bear any statement that is false or misleading in any way and shall not represent that the investigational product is safe or effective for the purposes for which it is being investigated.

11. Clinical trials monitoring and oversight activities.- (1) CSC, through its nominated officials, shall conduct random inspections of the clinical trial, BA and BE study sites to monitor compliance to the approved study protocol and monitoring plan of the sponsor.

(2) In order to assure the safety and protection of human subjects and quality of investigation, an effective procedure for on-site and centralized monitoring of clinical investigations must be developed and implemented by the sponsor, in accordance with Pakistan GCP guidelines and ICH-GCP guidelines.

(3) It should be assured that trial monitoring personnel are competent enough to perform their duties and are trained in monitoring, auditing, recording, analyses and reporting of clinical trials in accordance with Pakistan GCP guidelines and ICH-GCP guidelines. Risk-based approach should be opted for monitoring of clinical investigation.

(4) Monitoring plan should prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results.

(5) The following types of data and processes should ordinarily be identified as critical, namely:-

- (a) verification that informed consent was obtained appropriately;
- (b) adherence to protocol eligibility criteria designed to exclude individuals for whom the investigational product may be less safe than the protocol intended and to include only subjects from the targeted study population for whom the test article is most appropriate;
- (c) procedures for documenting appropriate accountability and administration of the investigational product e.g., ensuring the integrity of randomization at the site level, where appropriate;

- (d) conduct and documentation of procedures and assessments related to study endpoints protocol-required safety assessments, evaluating, documenting, and reporting serious adverse events and unanticipated adverse device effects, subject deaths and withdrawals, especially when a withdrawal may be related to an adverse event;
- (e) conduct and documentation of procedures essential to trial integrity; and
- (f) conduct and documentation of reconciliation of Investigational Products.

12. Review and report of safety information.- (1) The sponsor shall promptly review and report to the CSC, all information relevant to risk-benefit assessment and the safety of the investigational product, obtained during the investigation or otherwise received from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the DRAP.

(2) The sponsor or approval holder shall inform the DRAP in a written investigational medicinal product safety report, for any;

- (a) adverse experience associated with the use of the investigational product that is both serious and unexpected; or
- (b) finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. The reports shall be made as soon as possible and in not later than fifteen days after the initial receipt of the information. Each written report may be submitted to DRAP in a narrative format and shall bear prominent identification of its contents, *i.e.*, "investigational medicinal product safety report." If DRAP determines that additional data are needed, the sponsor or approval holder, may require further data to be submitted.

(3) All serious adverse events should be reported immediately to the DRAP.

(4) In each written investigational medicinal product safety update report, the sponsor shall identify all safety reports previously filed with the investigational medicinal product concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

(5) CSC may request a sponsor to submit investigational medicinal product safety update report in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the CSC which is responsible for review of the Investigational Product.

13. Clinical studies committee.- (1) The DRAP, with the approval of Federal Government, shall notify a clinical studies committee, consisting of the following members, namely:-

- (a) Director, Division of Pharmacy Services, DRAP, who shall be its ex-officio Chairman;
- (b) Additional Director or Deputy Director, Division of Pharmacy Services, DRAP, who shall be its ex-officio Secretary;
- (c) Chairman, Pakistan Health Research Council or his nominee who may be directly involved in conduct of clinical trials or having experience of conducting clinical trials;
- (d) one clinical pharmacist, from a renowned hospital, having at least five years of experience, to be nominated by the Authority;
- (e) one professor of pharmacology, to be nominated by the Authority;
- (f) one professor of pharmacy, having background of bio-pharmaceutics to be nominated by the Authority;
- (g) one clinician or physician or medical specialist having at least fifteen years of experience, to be nominated by the Authority;
- (h) one statistician, having background of designing and evaluating clinical studies with five years of experience or pharmaceutical professional having five years of experience in educational or professional services or practice of statistics, to be nominated by the Authority;
- (i) one representative of Pakistan pharmaceutical manufacturer association and the pharma bureau, each having fifteen years of experience and expertise of conducting clinical trials and BA or BE studies, to be nominated by the Authority as observer; and
- (j) co-opted member to be nominated by the committee for therapeutic goods or any other specific matter.

(2) The members, other than ex-officio members, of the CSC shall hold office for a period of three years and shall be eligible for re-nomination for one more time.

(3) The quorum to constitute a meeting of the CSC shall not be less than five members.

(4) The CSC shall perform the following functions, namely:-

- (a) screening, assessment, review and evaluation of applications for license of clinical trials, clinical trial sites, BA or BE studies, center and CRO;

- (b) screening, assessment, review and evaluation of applications for approval or registration of clinical trials and BA or BE studies;
 - (c) inspection of the premises prior to grant of license, approval of clinical trial, BA or BE study and during and after the completion of the trial or study, if so desired, by a panel constituted by the CSC and any co-opted member under sub-rule (6) of rule 13, any site where clinical trial and BA or BE study is planned to be conducted, to satisfy itself of the observance of conditions, guidelines or criteria as notified by the DRAP;
 - (d) grant, reject or suspend approval of a clinical trial and BA or BE study;
 - (e) grant, reject or suspend a license to center, clinical trial site, CRO and laboratory.
 - (f) evaluate the continuing review report on clinical trials and BA or BE studies submitted periodically by the IRB, sponsor, CRO or investigator and centers, as the case may be.
 - (g) renewal or extension of approval or registration to a clinical trial and BA or BE study.
 - (h) renewal of license to center, clinical trial site, CRO and laboratory.
- (5) The CSC may constitute a sub-committee for the performance of any of its functions.
- (6) The CSC may co-opt any subject related expert person having vast experience in the relevant field for advice on any particular matter under consideration.
- (7) The meetings of the CSC may be held quarterly or at any time as may be required or on the written request of its Chairman, who may at any time call a meeting within a period of fifteen days if there is any urgent matter for its consideration.
- (8) The CSC shall also consider relevant clinical trial decisions, reports or other information from stringent regulatory authorities and regional or international bodies like WHO, ICH and others. Any application for approval or registration of clinical trial will not undergo in the assessment process, if the same at any stage, has already been rejected, suspended or put on hold due to any reason, in ICH member countries or stringent regulatory authorities and shall be rejected during the process of screening.
- (9) The CSC may delegate any of its powers to Chairman of the Committee in writing with appropriate justification.

14. Prohibitions.- (1) No one can operate as CRO, clinical trial site, BA and BE center, laboratory, in Pakistan without prior approval from the CSC.

(2) No clinical trial and BA or BE studies shall be conducted except with the prior permission of the CSC, in accordance with the conditions as prescribed under rule 8.

(3) No clinical trial or study and BA or BE studies shall be conducted after the expiry of the authorized period except with the prior permission of the CSC, in accordance with the conditions as may be prescribed.

(4) No proceeding can be continued even within the grace permissible period under intimation to the CSC, if the ongoing trial is reported or found to be a contravention of any provision of these rules for getting authorization on the basis of false submissions.

(5) No clinical trial or BE studies shall be allowed to continue if the conditions to the approved protocol were violated in terms of variation without permission of the CSC.

15. GCP, GLP and BA or BE guidelines.- The DRAP shall adapt the ICH–GCP guidelines and also the GLP, BA or BE guidelines as per WHO, ICH and other international standards, which describe the criteria for the conduct of clinical trials and BA or BE studies following good clinical practice and good laboratory practice principles:

Provided that the DRAP shall revise or upgrade these guidelines from time to time, in compliance with the international standards.

16. Cancellation or suspension of license and approval.- (1) If the license holder or clinical trial, BA or BE study approval holder, as the case may be, does not comply with any of the conditions of the approval under these rules or violates any of the provisions of the Act or the Drug Act, 1976, (XXXI of 1976) or relevant rules and regulations made thereunder, the CSC, after giving an opportunity of hearing, may cancel or suspend the license or approval, as the case may be, for such a period as it thinks fit, by an order in writing, stating the reasons thereof.

(2) If at any time, for safety reason or any other ground a clinical trial is withdrawn or suspended anywhere in the world, the sponsor in Pakistan shall, forthwith, inform CSC, all participating investigators and all reviewing institutional review boards, together with the reasons for such withdrawal or suspension, within seven calendar days. The inventories of the investigational products shall be maintained and its safe custody shall be ensured.

(3) The CSC on having information with regard to the safety of the subject or any other ground, after giving an opportunity of personal hearing to the registration or approval holder, may at its own motion withdraw or suspend the clinical trial.

(4) The stocks of the investigational products so recovered or recalled shall be returned to the sponsor or otherwise disposed of, as the CSC may allow.

(5) When a license or approval for clinical trial, BA or BE study, as the case may be, is cancelled or suspended, an entry to that effect shall be recorded on the license and also in the register established for the purpose kept in office of Director, Pharmacy Services Division of the DRAP.

17. Complaint handling.- The CSC, upon receiving of complaint and after having inquiry into the matter, is satisfied, that the public interest so requires, may take action under rule 13 against license holder or approval holder, as the case may be.

18. Personal hearing.- Personal hearing shall be permissible before the CSC if;

(a) proceeding for canceling or suspending or revision of condition of license or modification of a license or approved clinical trial or study, as the case may be, under these rules; and

(b) license holder, clinical trial or study approval holder requires any, as the case may be.

19. Clinical trial under grant in aid.- Where an application for grant in aid is made under the Drugs (Research) Rules 1978, and the applicant submits evidence to this effect, no fee under these rules shall be required. However, the study shall be subject to all the conditions, guidelines or criteria as notified by the DRAP under these rules, approval from the CSC and such further conditions as may be imposed by the Committee of Experts on Drug Research constituted under the Drugs (Research), Rules 1978.

20. Clinical trial registry.- (1) Clinical trial registry means an official catalog, containing publicly accessible record of approved clinical trials.

(2) DRAP shall maintain clinical trial registry for approved clinical trials involving human subjects, being conducted in Pakistan.

(3) The clinical trial registry of Pakistan shall be a primary registry, which may in future, be linked to the registry network of the International clinical trials registry platform of the

WHO (WHO-ICTRP). It shall be a not-for-profit registry, with free and open access to researchers, clinicians, and the general public.

21. Trial subject registry.- A verifiable record of the clinical trial participants or subjects be maintained to stop duplicate enrolment and also to improve both patient safety and preserve data integrity of clinical trials. The subject identification shall be a closed information from the investigator, directly submitted to the DRAP.

22. Jurisdiction.– (1) The CSC may, for contravention of any provision of these rules, may recommend prosecution to the Federal Government before referral of the matter to the Drug Court for criminal adjudication.

(2) The CSC shall afford adequate opportunity of hearing to a person under these rules.

23. Appeal. – (1) A person who is aggrieved of the decision of the CSC shall file an appeal in writing within thirty days to the Authority, including,–

- (a) refusal to issue or renew a license;
- (b) decision to suspend or revoke a license;
- (c) refusal to approve, cancel or suspend a clinical trial, BA or BE study
- (d) order of closing down or making improvements in the clinical research organization or center or clinical trial site or laboratory;
- (e) order relating to equipment, apparatus, appliances, or other things at a CRO or center or clinical trial site or laboratory; or
- (f) imposition of fine.

(2) The CRO or center or clinical trial site or laboratory shall provide legal aid to a person, working in the aforesaid establishment, pertaining to the matters related to these rules.

Appendix – A

Form -I

[See rule 3]

Application for license to act as center, clinical trial site, CRO or laboratory

I/we

NIC number.....of M/s

business address and telephone number and fax number.....

.....

hereby apply for grant of license to the site for centers or clinical trial site or CRO or laboratory, situated

at

2. Type of the site meant for (whichever is applicable):-

- (i) Bio-equivalence and Bio-availability studies
- (ii) CRO
- (iii) Laboratory
- (iv) Clinical trials-
 - (a) Phase I
 - (b) Phase II
 - (c) Phase III
 - (d) Phase IV

3. I enclose:-

- (a) Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).
- (b) Details of premises including layout plan of the site.
- (c) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.
- (d) Names and qualifications of the above sections along with their staff.
- (e) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.,

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Date:.....

Name of the applicant

Signature

Seal of the firm/Company

Form – II
[See rule 7]

Application for approval and registration of clinical trial

I/we
NIC numberof M/sbusiness address
and telephone number and fax number.....hereby apply for approval or registration of clinical
trial, titled..... as per detail below:

- (1) Name of Investigational product, including all available names; trade, generic or INN name
etc.
- (2) Purpose of trial defining the indication along with the anticipated cost of the project and
sources of fund.....
- (3) Phase of the clinical trial to be conducted and its proposed duration.....
- (4) Proposed center for trial.....
- (5) List of participating countries.....
- (6) Investigator brochure along with summary.....
- (7) Pre-clinical, clinical data, safety studies.....
- (8) Final protocol.....
- (9) Detail of the investigator (Principal investigator and others along with CVs.....
- (10) IRB approval.....
- (11) Ethical committee composition (names and designations).....
- (12) Site approval by the Ethics committee.....
- (13) Informed consent (English and Urdu).....
- (14) Summary protocol or synopsis (Investigational Product).....
- (15) Adverse Event Reporting Form or CIOMS Form.....
- (16) Name of the monitors or clinical research associate.....
Evidence of registration in country of origin (GMP certificate along with CoPP or
Free sale
certificate).....
- (17) Copy of registration letter if registered in Pakistan.....
- (18) Proposed label of investigational product.....
- (19) Quantity of investigational products to be used in the trial along with justification
(Note: All the quantities of the investigational product should be procured from one single source)

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Date:

Name of the applicant

Signature

Seal of the firm/Company

Form – IIA
[See rule 7]

Application for approval and registration of bioequivalence or bioavailability study

I/we
CNIC numberof M/s business
address and telephone number and fax number.....hereby apply for approval and registration
of BA or BE study, titledas per detail below:

- (1) Name of Investigational Product (including all available names; trade, generic or INN name, chemical code etc.).....
- (2) Dosage Form of Investigational Product
- (3) Formulation of Investigational Product
- (4) Pharmacodynamics and Pharmacokinetics of Investigational Product
- (5) Purpose of study defining the indication along with the anticipated cost of the project and sources of fund.....
- (6) Proposed center for study.....
- (7) Investigational design and study plan.....
- (8) Pre-clinical or clinical data or safety studies.....
- (9) Final protocol.....
- (10) Detail of the investigator (Principal investigator, analysts and others along with CV)
- (11) IRB approval.....
- (12) Ethical committee composition (names and designations).....
- (13) Site approval by the Ethics committee.....
- (14) Informed consent (English and Urdu).....
- (15) Summary of the protocol or synopsis (Investigational Product).....
- (16) Adverse Event Reporting Form.....
- (17) Name of the monitor or clinical research associate.....
- (18) Evidence of registration in country of origin (GMP certificate along with CoPP or Free sale certificate).....
- (19) Copy of registration letter if registered in Pakistan.....
- (20) Proposed label of investigational product.....
- (20) Quantity of investigational product to be used in the study along with justification
(Note: All the quantities of the each of investigational product should be procured from one single source)

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Date:

Name of the applicant

Signature

Seal of the firm/Company

Form -III
[See rule 6]

Application for renewal of license to act as center, clinical trial site, CRO or laboratory

I/we
NIC numberof M/s
.....
Business address and telephone number and fax number.....
.....
hereby apply for renewal of license for center or clinical trial site or CRO or laboratory.

2. Type of the studies meant for:-

- (v) Bio-equivalence and Bio-availability studies
- (vi) CRO
- (vii) Laboratory
- (viii) Clinical trials-
 - (e) Phase I
 - (f) Phase II
 - (g) Phase III
 - (h) Phase IV

3. I enclose:-

- (f) Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their address, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors.
- (g) Details of premises including lay out plan of the site.
- (h) Details of the section wise equipment and machinery for required for the analytical or bio-analytical and clinical studies.
- (i) Name and qualifications of the management, and
- (j) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Date:.....

Name of the applicant

Signature

Seal of the firm/Company



**Drug Regulatory Authority of Pakistan
Government of Pakistan**

License to act as Bio-equivalence or Bioavailability study center

M/s
is/ are hereby licensed to act as center at the premises situated at

(2) This license shall be subject to the following and in addition to the conditions as specified under Rule 04:-

- (i) The license shall be valid for the period of three years from the date of issue unless earlier suspended or cancelled.
- (ii) The licensee shall maintain the conditions of GCP and GLP.
- (iii) Minimum safety standards shall be observed by the licensee.
- (iv) The Licensee shall develop SOPs for the conduct of studies and get formal approval from the DRAP.
- (v) The Licensee shall maintain adequate arrangement for storage of the study material as per protocol of the study.
- (vi) The licensee shall ensure that the study material is kept in containers bearing labels indicating the purposes including the security codes for which it has been kept.
- (vii) The licensee shall use the investigational product manufactured under the license exclusively for the experimental purpose and shall carry out the experimental work at specifically authorized premises.
- (viii) The licensee shall allow any member of the Central Licensing Board, Registration Board, Provincial Quality Control Board, CSC or any other official to enter, with or without notice, to the premises to satisfy himself that conditions of the license is being met during the study.
- (ix) The licensee shall comply with such further requirements, if any as may be specified from time to time either defined under these rules or any rule subsequently made.
- (x) The licensee shall develop mechanism for disposal of clinical study material or chemical as per defined procedure under rules and ICH guidelines.

(3) Name of approved expert staff:

Date of issue:

Secretary

Chairman

CSC

(Seal)

CSC



**Drug Regulatory Authority of Pakistan
Government of Pakistan**

**License to act as Contract Research Organization or Clinical Trial Site
or Laboratory**

M/s

is / are hereby licensed to act as CRO/ Clinical trial site/Laboratory at the premises
situated at

2. This license shall be subject to the following and in addition to the conditions
as specified under Rule 04:-

- (i) The license shall be valid for the period of three years from the date of issue unless earlier suspended or cancelled.
- (ii) The licensee shall maintain the conditions of GCP and GLP.
- (iii) Minimum safety standards shall be observed by the licensee.
- (iv) License holder shall develop Protocols or SOPs for the conduct of studies or trials and get formal approval from the DRAP.
- (v) License holder shall maintain adequate arrangement for storage of the study material as per protocol of the study.

3. Name of approved expert staff:

Date of issue:

Secretary

CSC

Chairman

CSC

(Seal)



Drug Regulatory Authority of Pakistan
Government of Pakistan

Approval to conduct the clinical trial, BA or BE study	
Reference No.:	Dated:
M/s..... is/are hereby authorized to conduct the clinical trial or study as detailed below at site or in such other place as the approving authority may from time to time authorize.	
(1) Title of trial or study:	
(2) Control number:	
(3) Approved protocol version:	
(4) Phase of trial or type of study:	
(5) Purpose of trial or study:	
(6) Investigational products; (a) Chemical name (b) Non-proprietary name (c) Trade name (if any) (d) Manufacturer	
(7) Applicant details; (a) Name (b) Designation	
(8) Principal investigators:	
(a) Name	(e) CNIC No.
(b) Position	
(c) Institute	
(d) Site	
(9) No. of patients to be enrolled:	
(10) Maximum duration of trial or study:	
(11) Further conditions, if any:	

Date of issue:

Secretary**Chairman**

CSC

(Seal)

CSC

Appendix – B

Checklist for Clinical Trial or Study Application

S. No.	Required Documents
(1)	Application on prescribed form along with Fee
(2)	Investigator Brochure
(3)	Final Protocol
(4)	Informed consent form (English and Urdu)
(5)	List of participating countries (If applicable)
(6)	Phase of trial
(7)	Quantity of Investigational Product to be imported or procured
(8)	Site of the trial
(9)	C.V of investigator
(10)	Ethical committee approval with complete composition of committee i.e Name and designations of the members
(11)	Approval from National Bio-ethics Committee (PHRC)
(12)	GMP certificate along with Free Sale Certificate or Certificate of Pharmaceutical Product (For locally manufactured product GMP Cert., COA of the Product and Registration Letter will be required)
(13)	Pre-clinical, clinical data and safety studies.
(14)	Summary of the protocol
(15)	Summary of the Investigator Brochure
(16)	Adverse Event Reporting form
(17)	No. of Patients to be enrolled in each center
(18)	Name of monitors or clinical research associate
(19)	Evidence of registration in country of origin
(20)	Copy of registration letter (if registered in Pakistan)
(21)	Sample of label of Investigational Product
(22)	Duration of trial

{File No.13-1/2017 DD (PS)}

(Sheikh Ansar Ahmad)
Director, Pharmacy Services Division
Drug Regulatory Authority of Pakistan, Islamabad